

The great gamble of COVID-19 vaccine development

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We are over six months into the consequences of the SARS-Co-V2 pandemic in the United States. Patients, families and doctors are frightened, weary and frustrated by the lack of support from regulatory agencies — the National Institutes of Health, Food and Drug Administration, Department of Health and Human Services, Centers for Medicare and Medicaid Services, Centers for Disease Control and Prevention, and state medical and pharmacy boards — for medical prophylaxis and treatment of COVID-19.

Warnings and barriers have prevented hundreds of thousands of patients from being treated at home with appropriate non-labelled use of off-target antivirals (zinc, hydroxychloroquine, azithromycin, doxycycline), steroids (dexamethasone, prednisone, budesonide, colchicine), and antithrombotics (low-molecular weight heparin, oral anticoagulants). It has become apparent that America has adopted a late-illness hospitalization model while waiting patiently and painfully for the panacea of a COVID-19 vaccine.

For months now the business news cycle has been popping with stories about vaccine development. “Operation Warp Speed” is an impressive effort supercharged with around \$10 billion in federal dollars spent with big pharma such as Merck, Pfizer, JNJ and AstraZeneca, and little biotech companies such as Moderna, Emergent Biosolutions, ApiJect and Panacea Biotec for vaccine development and commercialization. The potential financial windfall has spurred innovations with patents and royalty agreements applied or awarded to both private and government employees.

Many countries besides the U.S. are involved, including Canada, the United Kingdom, France, Israel, China and others. Funding has been allocated through direct grants, purchasing agreements and distribution systems. On May 15, 14 vaccine candidates were announced. Russia drew a strong reprisal from U.S. vaccine stakeholders when Vladimir Putin jumped ahead to recently announce the approval and use of the first COVID-19 vaccine. The public has been dazzled with depictions of viral vectors, messenger RNA derivatives, antibody responses and cellular immunity models.

We've learned much about COVID-19 and immunity in just a few months. The virus uses a spike protein on its surface to gain access to the respiratory epithelial cells and then into the body. Diagnostic labs can measure antibodies (IgG, IgM) in blood directed against the spike protein and the viral nucleocapsid. While these antibodies against the spike protein neutralize the virus in the test tube, it is a different, unmeasured family of antibodies (IgA) produced in the mucous membranes that actually defends against the inhaled virus in people who are newly immune after recovery from COVID-19.

Antibody production after COVID-19 takes a few weeks to ramp up but wanes fairly quickly after several weeks to months. Thus, the hope is that a vaccine could instill permanent memory in antigen-presenting T-cells that would remind the plasma cells and B-cells to proliferate and restore antibody production more quickly in the setting of re-inoculation. The science is not clear on whether a vaccine can stimulate rapid IgA production for quick protection or whether it can permanently imprint the immune system for durable immunity. Many details need to be worked out, including the initial administration and booster schedule, vaccine dose, route of administration (intranasal, oral, injection) and confirmation of safety.

These questions have set up one of the greatest gambles in modern history with billions of dollars spent, hundreds of thousands of lives lost, and unimaginable misery, heartbreak and human suffering by foregoing early medical treatment and waiting for the advent of the vaccine. The allure of a definitive solution for the large population still at risk for infection and the potential windfall for stakeholders have converged into a single inexorable force.

The headwinds for vaccine development are prodigious. The big Phase 3 clinical trials are designed to recruit previously uninfected persons; however, given large numbers of asymptomatic cases and unreliable antibody tests, the vaccine/placebo may have no differential impact on a large group of younger subjects enrolled. Patients may reject “challenge studies” because they are fearful of being exposed to the infection intentionally while getting the placebo. There may be early (injection site reactions, fever) and late (autoimmune, neurodegenerative) safety events. Lastly, and most importantly, the vaccines may simply be modestly effective — meaning there is partial immunity but no guarantee of freedom from future infection.

What are the likely end-scenarios? First, safe and effective vaccine(s) are commercialized soon, large populations are saved and stakeholders get their returns. Second, safe but partially or minimally effective vaccine(s) come forward and there is a struggle over benefits and risks with tepid uptake and commercialization. Third, despite impressive results in the test tube, the vaccine trials cannot demonstrate statistically significant reductions in bona fide COVID-19 infections and none is approved for use. Fourth, any of the above scenarios, but the result comes so late that herd immunity has sufficiently developed, infection rates have waned, or virulence has dropped and there simply is not a market for these products.

My prediction is that vaccines indeed will become a reality, as in Russia, but they will be hurried to market only to be partially effective and the uptake and population benefit will remain uncertain given all the issues discussed.

In the meantime, many doctors on the front lines and in clinics continue to press regulators for unrestricted use of any and all available medications to treat COVID-19 patients at home. Every day of vaccine development means more hospitalizations and deaths. Caregivers, unlike government officials and biotechnology executives, are terrible gamblers. They are trained to take calculated risks and prescribe drugs they know have a basis to work early with COVID-19.

Vaccine stakeholders, including government agencies, should not hold up treatment now in the gamble for a future panacea — even if it comes at “warp speed.”

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